PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 207/34, A61K 31/40

A1

(11) International Publication Number: **WO 00/06542**

(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/EP99/05349

(22) International Filing Date: 21 July 1999 (21.07.99)

(30) Priority Data:
9816653.1 30 July 1998 (30.07.98) GB

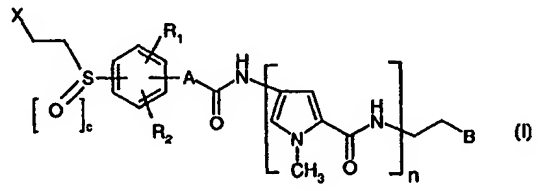
(71) Applicant: PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milan (IT).

(72) Inventors: COZZI, Paolo; Via Zanella, 48/5, I-20133 Milan (IT). CALDARELLI, Marina; Via Besenzanica, 9, I-20147 Milan (IT). BERIA, Italo; Via G. Matteotti, 39, I-45030 Villamarzana (IT). GERONI, Maria, Cristina; Via Correggio, 48, I-20149 Milan (IT). CAPOLONGO, Laura; Via P. Rembrandt, 11, I-20147 Milan (IT).

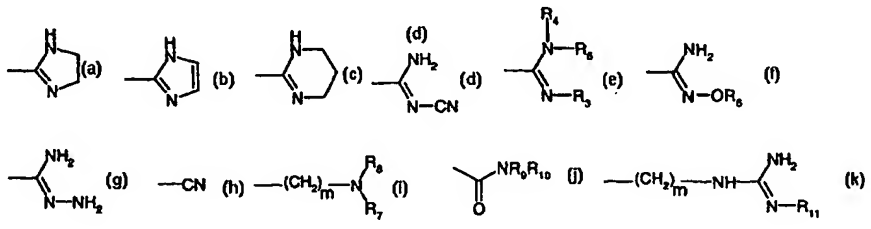
(81) Designated States: JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: OXIDISED SULFURATED DISTAMYCIN DERIVATIVES, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AGENTS



(I)



(57) Abstract

Compounds which are oxidised sulfurated distamycin derivatives of formula (I) wherein n is 2, 3 or 4; c is 1 or 2; A is a bond, a C_1–C_4 alkylene or C_2–C_4 alkenylene group; R_1 and R_2, which are the same or different, are selected from hydrogen, C_1–C_4 alkyl optionally substituted by one or more fluorine atoms, and C_1–C_4 alkoxy; X is a halogen atom; B is selected from L: (a), (b), (c), (d), (e), (f), (g), (h), (i), (j) and (k); wherein R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10}, which are the same or different, are selected from hydrogen or C_1–C_4 alkyl; R_{11} is hydrogen, C_1–C_4 alkyl or hydroxy, and m is 0, 1 or 2; or pharmaceutically acceptable salts thereof; are useful as antitumor agents.

FOR THE PURPOSES OF INFORMATION ONLY

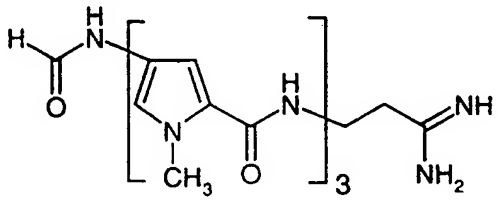
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

OXIDISED SULFURATED DISTAMYCIN DERIVATIVES, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AGENTS

The present invention relates to new alkylating antitumor agents analogous to Distamycin A, to a process for their preparation, to pharmaceutical compositions containing them and to their use as therapeutic agents.

Distamycin A, whose formula is reported below



belongs to the family of the pyrroleamidine antibiotics and it is reported to interact reversibly and selectively with DNA-AT sequences, thus interfering with both replication and transcription. See, for a reference, Nature, 203, 1064 (1964); FEBS Letters, 7 (1970) 90; Prog. Nucleic Acids Res. Mol. Biol., 15, 285 (1975).

Several analogous to distamycin are known in the art.

DE-A-1795539 discloses distamycin derivatives in which the formyl group is replaced by a hydrogen atom or by the carboxylic acid residue of a C_1-C_4 aliphatic or cyclopentylpropionic acid.

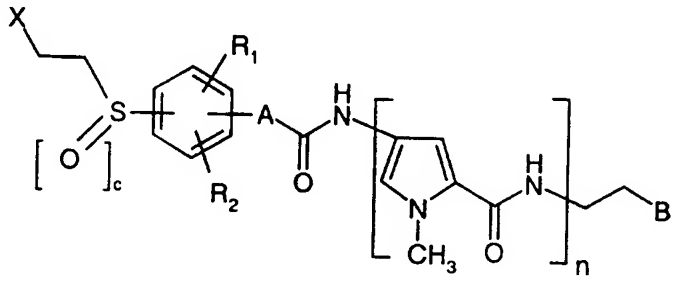
EP-A-246,868 describes distamycin analogues in which the distamycin formyl group is substituted by aromatic, alicyclic or heterocyclic moieties bearing alkylating groups.

WO 97/28123 and WO 97/43258 describe distamycin analogues in which the amidino group is replaced with different nitrogen-containing ending groups and the distamycin formyl group is substituted by an aromatic or a cinnamoyl moiety, respectively.

It has now been found that a new class of distamycin derivatives as defined hereinunder, wherein the distamycin formyl group is substituted by a phenylcarbonyl, phenylalkylcarbonyl or phenylalkenylcarbonyl group bearing

a haloethyl-sulfinyl or a haloethyl-sulfonyl group as an alkylating moiety, and the amidino group is optionally replaced by various nitrogen-containing ending groups, shows valuable biological properties.

Therefore, the present invention provides compounds which are oxidised sulfurated distamycin derivatives of formula:



(I)

wherein:

n is 2, 3 or 4;

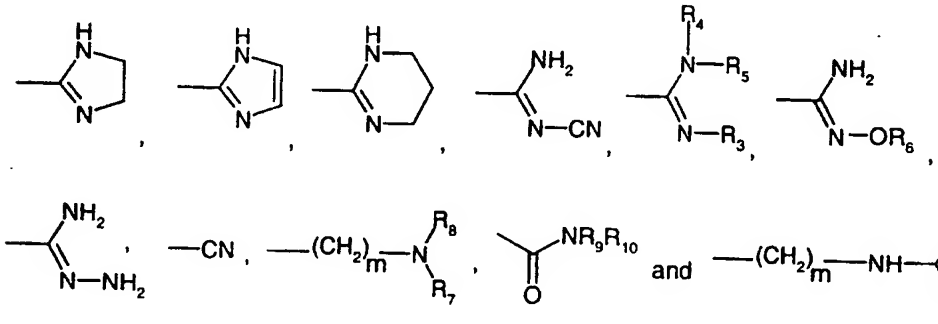
c is 1 or 2;

A is a bond, a C_1-C_4 alkylene or C_2-C_4 alkenylene group;

R_1 and R_2, which are the same or different, are selected from hydrogen, C_1-C_4 alkyl optionally substituted by one or more fluorine atoms, and C_1-C_4 alkoxy;

X is a halogen atom;

B is selected from:



wherein R_3, R_4, R_5, R_6, R_7, R_8, R_9 and R_{10}, which are the same or different, are selected from hydrogen or C_1-C_4 alkyl; R_{11} is hydrogen, C_1-C_4 alkyl or hydroxy, and m is 0, 1 or 2;

or pharmaceutically acceptable salts thereof.

The present invention includes within its scope also all the possible isomers covered by the compounds of formula (I), both separately and in admixture, as well as the metabolites and the pharmaceutically acceptable bio-

precursors (otherwise known as pro-drugs) of the compounds of formula (I).

In the present description, unless otherwise specified, both terms alkyl and alkoxy include straight or branched C_1-C_4 alkyl and alkoxy groups such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy.

Preferred C_1-C_4 alkyl or alkoxy groups are methyl, ethyl, methoxy and ethoxy groups.

When substituted by one or more fluorine atoms, the C_1-C_4 alkyl groups are preferably C_1-C_4 perfluoroalkyl groups, e.g. trifluoromethyl.

Both terms alkylene and alkenylene refer, respectively, to C_1-C_4 alkylene or C_2-C_4 alkenylene groups, as bivalent radicals of the corresponding C_1-C_4 saturated or C_2-C_4 unsaturated hydrocarbons.

Preferred alkylene or alkenylene groups according to the present invention are methylene, ethylene or vinylene groups.

The term halogen atom includes fluorine, chlorine, bromine and iodine, being chlorine and bromine preferred.

Within the compounds of formula (I) the haloethyl-sulfinyl or sulfonyl group and the A group are in ortho, meta or para position with respect to each other; preferably, they are in meta or para position.

Pharmaceutically acceptable salts of the compounds of formula (I) are their salts with pharmaceutically acceptable either inorganic or organic acids such as, for instance, hydrochloric, hydrobromic, sulfuric, nitric, acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic and p-toluenesulfonic acid.

A preferred class of compounds of the present invention is that wherein, in formula (I):

n is 3;

c is 1;

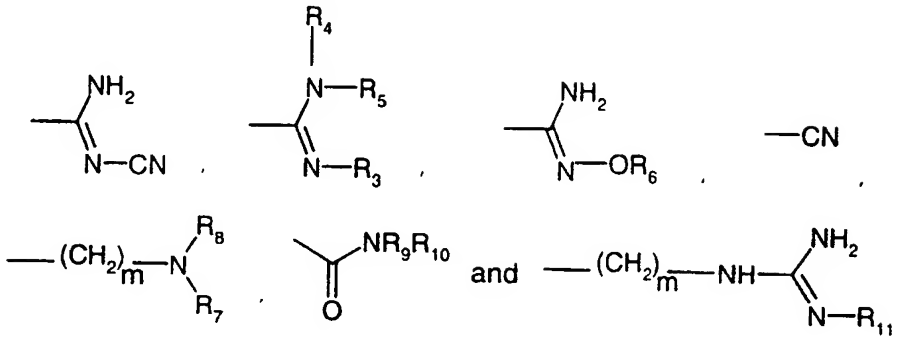
A is a bond or vinylene;

R_1 and R_2 which are the same or different, are selected from

hydrogen, methyl, methoxy or trifluoromethyl;

X is chloro or bromo;

B is selected from:



wherein R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and R_{11}, which are the same or different, are selected from hydrogen or methyl; R_6 is hydrogen; and m is 0 or 1;

or the pharmaceutically acceptable salts thereof.

Examples of specific compounds according to the present invention, especially in the form of salts, preferably with hydrochloric acid, are the following:

1) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

2) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

3) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

4) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N',N'-trimethylamidine;

5) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

6) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

7) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

8) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamide;

9) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

10) 2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;

11) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N-dimethylamine;

12) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-bromoethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

13) 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

14) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

15) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-

carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

16) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

17) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N,-dimethylamidine;

18) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

19) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

20) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

21) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

22) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

23) 2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;

24) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N,N'-trimethylamidine;

25)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

26)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

27)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

28)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

29)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

30)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

31)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

32)2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;

33)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

34)3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-

carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

35) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

36) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

37) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

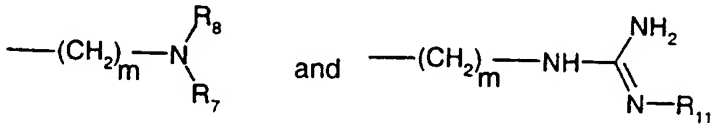
38) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

39) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

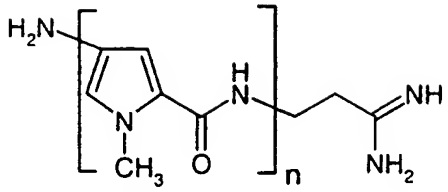
40) 2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine.

A further object of the present invention is a process for preparing the compounds of formula (I), and the pharmaceutically acceptable salts thereof, which process comprises:

(a) when B is other than

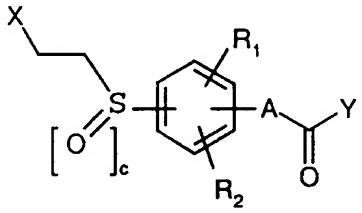


reacting a compound of formula:



(II)

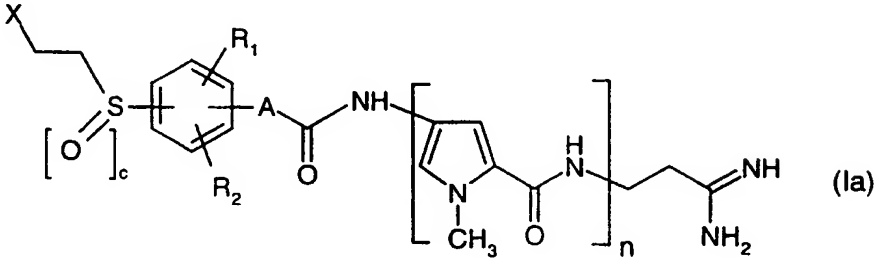
with a compound of formula:



(III)

wherein n, c, R_1, R_2, X and A are as defined above, and Y is hydroxy or a suitable leaving group;

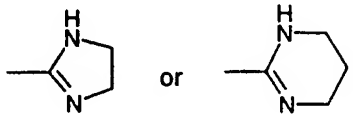
so as to obtain a compound of formula:



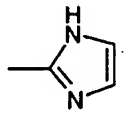
(Ia)

and, then, optionally reacting a compound of formula (Ia) with:

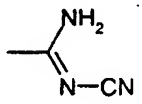
(i) $H_2N-(CH_2)_r-NH_2$, wherein r is 2 or 3, so as to obtain a compound of formula (I) having B equal to:



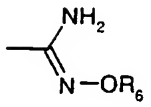
(ii) H_2N-CH_2-CHO, so obtaining a compound of formula (I) having B equal to:



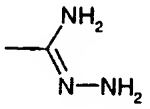
(iii) H_2N-CN, so obtaining a compound of formula (I) having B equal to:



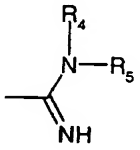
(iv) H_2N-OR_6, so obtaining a compound of formula (I) having B equal to:



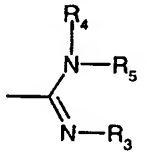
(v) H_2N-NH_2, so obtaining a compound of formula (I) having B equal to:



(vi) HNR_4R_5, so obtaining a compound of formula (I) having B equal to:



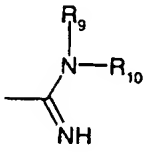
and then optionally with H_2NR_3, so obtaining a compound of formula (I) having B equal to:



(vii) succinic anhydride, so obtaining a compound of formula (I) having B equal to $-C\equiv N$;

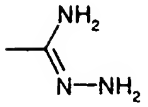
(viii) water in an alkaline medium, so obtaining a compound of formula (I) having B equal to $-CONR_9R_{10}$ wherein R_9 and R_{10} are both hydrogen atoms;

(ix) HNR_9R_{10}, so obtaining a compound of formula (I) having B equal to:

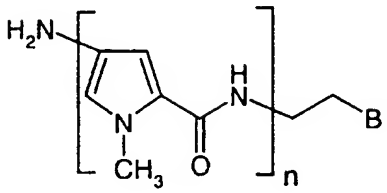


and then with water in an alkaline medium, so obtaining a compound of formula (I) having B equal to $-CONR_9R_{10}$, wherein R_9 and R_{10} are, each independently, hydrogen or C_1-C_4 alkyl; or

(b) when B is other than

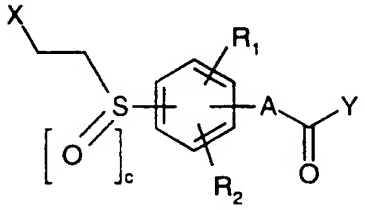


reacting a compound of formula:



(IV)

with a compound of formula:



(III)

wherein n, c, B, R_1, R_2, X, Y and A are as defined above; so obtaining the corresponding compound of formula (I); and, if desired, converting the compound of formula (I) into a pharmaceutically acceptable salt thereof.

In formula (III), Y is hydroxy or a leaving group selected, for instance, from chloro, 2,4,5-trichlorophenoxy, 2,4-dinitro-phenoxy, succinimido-N-oxy, imidazolyl group, and the like.

The condensation reactions as set forth above under processes (a) and (b) is carried out according to known methods, for instance those described in the aforementioned EP-A-246,868.

The reaction between a compound of formula (II) or (IV) with a compound of formula (III) is preferably carried out with a molar ratio (II):(III) or (IV):(III) of from 1:1 to 1:2.

Within the compounds of formula (III) wherein Y is hydroxy, the reaction is carried out in an organic solvent, such as, dimethylsulphoxide, hexamethylphosphotriamide, dimethylacetamide, dimethylformamide, ethanol, phenyl, or pyridine, in the presence of an organic or inorganic base such as triethylamine, diisopropyl ethylamine, or sodium or potassium carbonate or bicarbonate, and of a condensing

agent such as, N-ethyl-N'-(3-dimethylamino-propyl)-carbodiimide, N,N'-dicyclohexyl-carbodiimide, or 1-hydroxy-benzotriazole hydrate.

The reaction temperature may vary from about -10°C to about 100°C, and the reaction time from about 1 to about 24 hours.

Within the compounds of formula (III) wherein Y is a leaving group as set forth above, the aforementioned condensation reaction may be carried out in an organic solvent such as, for instance, dimethylformamide, dioxane, pyridine, tetrahydrofurane, or mixtures thereof with water, optionally in the presence of an organic or inorganic base, e.g. N,N'-diisopropylethylamine, triethylamine, sodium or potassium bicarbonate, at a temperature of from about 0°C to about 100°C, and for a time varying from about 2 hours to about 48 hours.

The reaction between a compound of formula (Ia) according to process (a) and one of the reactants as described above at points (i)-(vi) or (ix), can be carried out according to known methods, for instance those reported in US-4,766,142; WO 97/28123; Chem. Revs. 1961, 155; J. Med. Chem. 1984, 27, 849-857; Chem. Revs. 1970, 151; and "The Chemistry of Amidines and Imidates", edited by S. Patai, John Wiley & Sons, N.Y. (1975).

The reaction of a compound of formula (Ia) with succinic anhydride, as defined in point (vii) above, is preferably carried out with a molar ratio (Ia):succinic anhydride of from 1:1 to 1:3 in an organic solvent such as, for instance, dimethyl sulphoxide or dimethylformamide, and in the presence of an organic or inorganic base such as, e.g., triethylamine, diisopropylethylamine, sodium or potassium carbonate, and the like. The reaction temperature may vary from about 25°C to about 100°C, and the reaction time from about 1 hour to about 12 hours.

The reaction with water in an alkaline medium, as defined in points (viii) and (ix) above, may be carried out according to known methods usually employed for alkaline hydrolysis, for instance by treating the substrate with an

excess of sodium or potassium hydroxide in water or in a water/organic solvent admixture, e.g. dioxane, tetrahydrofuran, or acetonitrile, at a temperature of from about 50°C to about 100°C, for a time varying from about 2 hours to about 48 hours.

The compounds of formula (II) are known or may be prepared according to known methods; see, for a reference, Arcamone et al. in Gazzetta Chim. Ital. 97, 1097 (1967).

Also the compounds of formula (III) are known or may be prepared according to known methods, for instance by working as described in J. Org. Chem. 1993, 58, 4506-4508; Helvetica Chimica Acta, Vol. 67,(1984), 1316-1327; Tetrahedron Letters 35, 3457-3460, 1994; J. Chem. Soc. Perkin Trans. 1, 2961, 1991.

The compounds of formula (IV) are known compounds as well, for instance as reported in the aforementioned WO 97/28123.

In view of what above reported, it is clear to the man skilled in the art that when preparing the compounds of formula (I) as set forth above, optional amino groups, i.e. R_7 and/or R_8 of the compounds of formula (IV) equal to hydrogen, need to be properly protected according to conventional techniques, so as to avoid unwanted side reactions.

Likewise, the conversion of the said protected amino groups into the free amines may be carried out according to known procedures. See, for a general reference, J. Org. Chem. 43, 2285, (1978); J. Org. Chem. 44, 811 (1979); J. Am. Chem. Soc. 78, 1359 (1956); Ber. 65, 1192 (1932); and J. Am Chem. Soc. 80, 1154, (1958).

Salification of a compound of formula (I), as well as preparation of a free compound starting from a salt, may be carried out by known standard methods.

Well known procedures such as, e.g., fractional crystallisation or chromatography, may also be followed for separating a mixture of isomers of formula (I) into the single isomers.

The compounds of formula (I) may be purified by conventional techniques such as, e.g., silica gel or

alumina column chromatography, and/or by recrystallisation from an organic solvent such as, e.g., a lower aliphatic alcohol, e.g. methyl, ethyl or isopropyl alcohol, or dimethylformamide.

PHARMACOLOGY

The compounds of formula (I) according to the present invention are useful as antineoplastic agents.

In particular, the interest in the development of these molecules (hypoxia-selective cytotoxic agents) is related to their effect against tumor cell populations which grow at very low oxygen concentrations in solid tumors and which appear to limit the effectiveness of conventional chemotherapy.

The antineoplastic activity of the compounds was evaluated in vivo against advanced human mammary carcinoma xenograft (MX-1) showing a very good antitumor activity.

MX-1 human mammary (originally obtained from NCI, NHI, Bethesda, MD) was transplanted s.c. in athymic mice using 15-20 mg of tumor brei. The tumor model was maintained in vivo in adult female Hsd:athymic nude mice.

Nude mice were 4-6 weeks old, weighed 20-25 g and were maintained in cages with paper filter covers; food and bedding were sterilised and water was acidified (pH 2.5-3).

All animals were supplied by Harlan Nossan (Italy).

The mouse colony was routinely tested monthly for the absence of antibodies to a panel of pathogens including Mouse hepatitis, Sendai Virus and Mycoplasma pulmonis.

Drug activity was determined on advanced solid tumors (when tumor mass is > 500 mg); tumor growth was assessed by caliper measurement, and tumor weight was estimated according to Geran.

The antitumor effect was determined by comparing tumor weights in the treated group and those of the control group on a given day. The percentage of tumor growth inhibition (%T.I.) was calculated 7 days after the last treatment, according to the following equation:

100-(median tumor weight of treated group/median tumor weight of control group)x100

Tumor-free mice 90 days after tumor implant are considered cured mice.

Toxicity was evaluated on the basis of the body weight reduction and gross autopsy findings, mainly in terms of reduction of spleen and liver size.

All drug solutions were prepared immediately before use.

Treatment was administered (q4dx4) intravenously in a volume of 10 ml/kg of body weight.

The compounds of the invention can be administered to mammals, including humans, through the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally. The dosage depends on age, weight and conditions of the patient and on the administration route. For example, a suitable dosage for administration to adult humans may range from about 0.1 to about 150-200 mg pro dose 1-4 times a day.

Further object of the present invention are pharmaceutical compositions, which comprise a compound of formula (I) as an active principle, in association with one or more pharmaceutically acceptable carrier and/or diluent.

The pharmaceutical compositions of the present invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as a carrier, for example, sterile water or preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions for intramuscular injections may contain, together with the active compound a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

In the forms for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl cellulose, polyvinyl-pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulation. Said pharmaceutical preparations may be manufactured by known techniques, for example by means of mixing, granulating, tabletting, sugar-coating or film-coating processes.

Further object of the present invention are the compounds of formula (I) for use in a method for treating the human or animal body by therapy.

Furthermore, the present invention provides a method for treating tumors in a patient in need of it, which comprises administering to said patient a composition of the invention.

A further object of the present invention is a combined method for treating cancer or for ameliorating the conditions of mammals, including humans, suffering from cancer, said method comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumor agent, close enough in time and in amounts sufficient to produce a therapeutically useful effect.

The present invention also provides products containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumour agent as a

combined preparation for simultaneous, separate or sequential use in anti-cancer therapy.

The term "antitumor agent" is meant to comprise both a single antitumor drug and "cocktails" i.e. a mixture of such drugs, according to the clinical practice. Examples of antitumor agents that can be formulated with a compound of formula (I), or alternatively, can be administered in a combined method of treatment, include doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluoro-uracil, melphalan, cyclophosphamide, 4-demethoxy daunorubicin, bleomycin, vinblastin, and mitomycin, or mixtures thereof.

The following examples are given to better illustrate the present invention but do not limit the scope of the invention itself.

Example 1

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine

Step I: **The intermediate 4-(2-hydroxyethyl)thiobenzoic acid**

To a solution of 400 mg of 4-thiobenzoic acid in 2.85 ml of NaOH 2N, 0.160 ml of 2-chloroethanol were added. The solution was refluxed for 1 hour, 2.85 ml of hydrochloric acid 2N were then added dropwise and the precipitated was filtered and dried yielding 370 mg of a white solid.

FAB-MS: m/z 220, (60, $[M+H]^+$)

PMR ($CDCl_3$) d:

7.61 (d, J= 15.7 Hz, 1H), 7.33 (m, 2H), 6.55 (m, 2H), 6.21 (d, J= 15.7 Hz, 1H), 4.22 (q, J=7.1 Hz, 2H), 3.9 (b.s., 1H), 3.19 (q, J=7.1 Hz, 2H), 1.25 (t, J=7.1 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H).

By analogous procedures and by using the opportune starting materials the following intermediate compounds can be obtained:

3-methyl-4(2-hydroxyethyl)thiobenzoic acid;

4-(2-hydroxyethyl)thiocinnamic acid

FAB-MS: m/z 224

PMR (DMSO-d_6) d:

7.59 (m, 2H), 7.52 (d, J = 16.0 Hz; 1H), 7.31 (m, 2H), 6.46 (d, J= 16.0 Hz, 1H), 4.9 (bs, 1H), 3.57 (t, J=6.8 Hz, 2H), 3.08 (t, J=6.8 Hz, 2H).

Step II: **The intermediate 4-(2-chloroethyl)thiobenzoic acid**

A solution of 400 mg of the intermediate, as prepared in step I, and 1.18 ml of thionyl chloride in 15 ml of toluene were refluxed for four hours, then the solvent was evaporated in vacuo. The crude residue was dissolved in 20 ml acetonitrile/water (1/1) and warmed at 40°C for 1 hour. The solvent was then evaporated to dryness yielding 430 mg of a white solid which was used without further purification.

FAB-MS: m/z 216

PMR ($CDCl_3$) d:

8.01 (m, 2H); 7.38 (m, 2H); 3.67 (d, J = 7.0 Hz, 2H); 3.35 (d, J = 7.0 Hz, 2H).

By analogous procedures and by using the opportune starting materials the following compound can be obtained:

3-methyl-4(2-chloroethyl)thiobenzoic acid;

Step III: **The intermediate 4-(2-chloroethyl)sulfinylbenzoic acid**

A solution of 430 mg of the inermediate obtained from step II was added drpowise to a solution of 468 mg of $NaIO_4$ in 4.3 ml of water. The mixture was stirred at room temperature for 1 day, then at 80°C for 5 hours and subsequently dried under vacuum and purified by flash chromatogrphy (Ethylacetate/Exane:8/2) to yield 320 mg of the intermediate as a white solid.

By analogous procedures and by using the opportune starting materials the following compounds can be obtained:

3-methyl-4(2-chloroethyl)sulfinylbenzoic acid;

3-methyl-4(2-bromoethyl)sulfinylbenzoic acid;

4-(2-chloroethyl)sulfinylcinnamic acid.

Step IV: **The title compound**

86 mg of DCC were added to a solution of 106 mg of the intermediate obtained from step III in 4 ml of DMF and

cooled at 0°C. The solution was stirred at 0°C for 30 minutes then 200 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine dihydrochloride (prepared as reported in J. Med. Chem 32, 774-778, 1989) and 45 mg of potassium bicarbonate were added. The solution was stirred at room temperature for 3 hours then hydrochloric acid 2N was added up to pH acid.

The solvent was then removed in vacuo and the crude residue purified by flash chromatography (methylene chloride/ methanol=85/15) to yield 150 mg of the title compound as a white solid.

FAB-MS: m/z 668, (100, $[M+H]^+$)

PMR ($DMSO-d_6$) d:

10.56 (s, 1H), 10.00 (s, 1H), 9.92 (s, 1H), 9.0 (b.s., 2H), 8.6 (b.s., 2H), 8.21 (t, J=5.6 Hz, 1H), 8.14 (m, 2H), 7.83 (m, 2H), 7.35 (d, J=1.7 Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 4.0-3.8 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.49 (m, 2H), 3.46 (m, 2H), 3.26 (m, 2H), 2.61 (t, J=6.6 Hz, 2H).

By analogous procedures and by using the opportune starting materials the following compounds can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N',N'-trimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

carboxamido]propion-N-cyanamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamide;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;
2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N-dimethylamine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-bromoethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-

chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine.

Example 2

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine

Step I: **The intermediate 4-(2-chloroethyl)thiocinnamic acid**

To a solution of 150 mg of 4-(2-hydroxyethyl)thiocinnamic acid (prepared as reported in example 1 step I) in 3 ml of pyridine, 0.105 ml of mesyl chloride were added and the solution was warmed for 2 hours at 80°C. The solution was

cooled at room temperature and hydrochloric acid 37% was slowly added up to pH=1. The obtained precipitate was filtered and washed with water, then dried thus obtaining 100 mg of an orange solid.

FAB-MS: m/z 242

PMR (DMSO-d_6) d:

12.3 (bs, 1H); 7.63 (m, 2H); 7.54 (d, J = 15.9 Hz, 1H); 7.34 (m, 2H); 6.48 (d, J = 15.9 Hz, 1H); 3.76 (t, J = 7.1 Hz, 2H); 3.40 (t, J = 7.1 Hz, 2H).

By analogous procedures and by using the opportune starting materials the following products can be obtained:

4-(2-chloroethyl)thiobenzoic acid;

4-(2-bromoethyl)thiobenzoic acid;

3-methyl-4-(2-chloroethyl)thiobenzoic acid.

***Step II*: The intermediate 4-(2-chloroethyl)sulfinylcinnamic acid**

To 88 mg of $NaIO_4$ in 0.8 ml of water 90 mg of the intemediate obtained from step I, in 8 ml of MeOH, were added. The solution was warmed at 80°C for 5 hours then the solvent evaporated in vacuo. The residue was chromatographed on silica gel (Ethyl acetate/Exane:7/3) yielding 45 mg of a white solid.

***Step II*: The title compound**

A solution of 45 mg of 4-(2-chloroethyl)sulfinylcinnamic acid (prepared as described in step II), 35 mg of dicyclohexylcarbodiimide and 24 mg of 1-hydroxybenzotriazole hydrate in 3 ml of DMF, was stirred at 80°C for four hours, cooled at room temperature and then added with 90 mg 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine dihydrochloride (prepared as reported in J. Med. Chem 32, 774-778, 1989) and 17 mg of potassium bicarbonate.

The mixture was stirred at room temperature for 2 hours, the solvent was evaporated in vacuum and the crude residue purified by flash chromatography (methylene chloride/ methanol: 8/2) to yield 100 mg of the title compound as a yellow solid.

FAB-MS: m/z 694, (100, [M+H]$^+$)

PMR (DMSO-d_5) d:

10.38 (s, 1H), 9.98 (s, 1H), 9.92 (s, 1H), 8.8 (b.s., 4H), 8.22 (t, J=6.0 Hz, 1H), 7.80 (m, 2H), 7.74 (m, 2H), 7.55 (d, J=15.6 Hz, 1H), 7.32 (d, J=1.7 Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.98 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 6.93 (d, J=15.6 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.76-3.96 (m, 2H), 3.48 (m, 2H), 3.2-3.45 (m, 2H), 2.61 (t, J=6.5 Hz, 2H).

By analogous procedures and by using the opportune starting materials the following products can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N,-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-

carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;
2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N,N'-trimethylamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine.

Example 3

Tablets each weighing 0.250 g and containing 50 mg of the active substance can be manufactured as follows:

Composition for 10,000 tablets	
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride	500 g
Lactose	1,400 g
Corn starch	500 g
Talc powder	80 g
Magnesium stearate	20 g

The active substance, lactose and half of the corn starch were mixed; the mixture was then forced through a sieve of 0.5 mm mesh size.

Corn starch (10 g) was suspended in warm water (90 ml) and the resulting paste was used to granulate the powder. The granulate was dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and magnesium stearate was added, carefully mixed and processed into tablets.

Example 4

Capsules, each dosed at 0.200 g and containing 20 mg of the active substance can be prepared as follows:

Composition for 500 capsules	
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride	10 g
Lactose	80 g
Corn starch	5 g
Magnesium stearate	5 g

This formulation can be encapsulated in two-piece hard gelatin capsules and dosed at 0.200 g for each capsule.

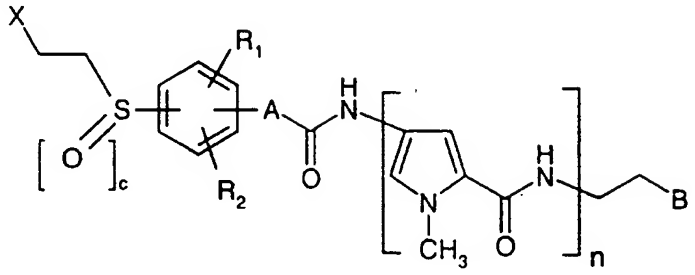
Example 5

Intramuscular Injection 25 mg/ml

An injectable pharmaceutical composition can be manufactured by dissolving 25 g of 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride in sterile propyleneglycol (1000 ml) and sealing ampoules of 1-5 ml.

CLAIMS

1. A compound which is an oxidised sulfurated distamycin derivative of formula:



(I)

wherein:

n is 2, 3 or 4;

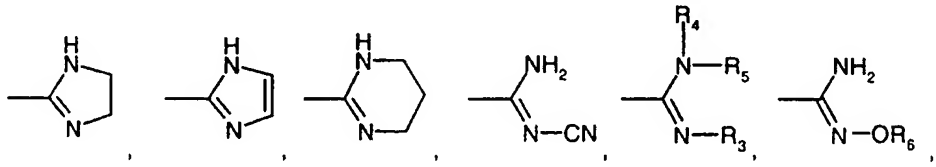
c is 1 or 2;

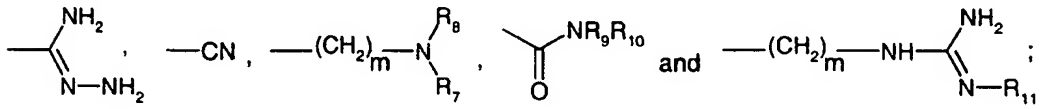
A is a bond, a C_1-C_4 alkylene or C_2-C_4 alkenylene group;

R_1 and R_2, which are the same or different, are selected from hydrogen, C_1-C_4 alkyl optionally substituted by one or more fluorine atoms, and C_1-C_4 alkoxy;

X is a halogen atom;

B is selected from:





wherein R_3, R_4, R_5, R_6, R_7, R_8, R_9 and R_{10}, which are the same or different, are selected from hydrogen or C_1-C_4 alkyl; R_{11} is hydrogen, C_1-C_4 alkyl or hydroxy, and m is 0, 1 or 2;

or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are, independently from each other, hydrogen, methyl or ethyl.

3. A compound according to claim 1 or 2 wherein

n is 3;

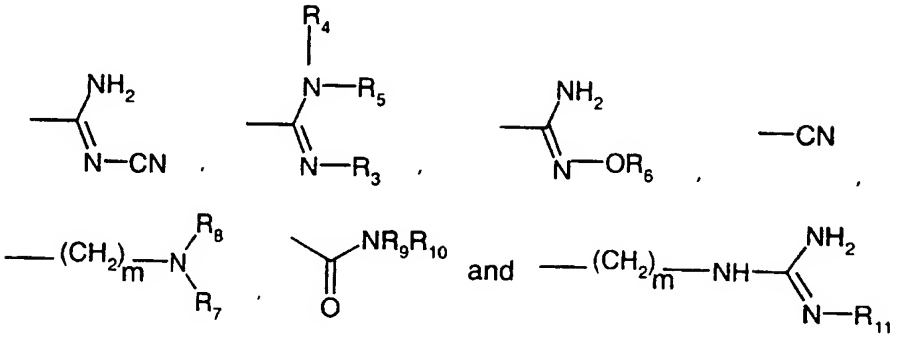
c is 1;

A is a bond or vinylene;

R_1 and R_2 which are the same or different, are selected from hydrogen, methyl, methoxy or trifluoromethyl;

X is chloro or bromo;

B is selected from:



wherein R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and R_{11}, which are the same or different, are selected from hydrogen or methyl; R_6 is hydrogen; and m is 0 or 1;

or the pharmaceutically acceptable salts thereof.

4. A compound selected from the group consisting of:

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N',N'-trimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-

carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N-dimethylamine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-bromoethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-(2-chloroethylsulfinyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N,-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfinyl)cinnamoyl-1-carboxamido]pyrrole-2-

carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N,N'-trimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)phenyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-cyanamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

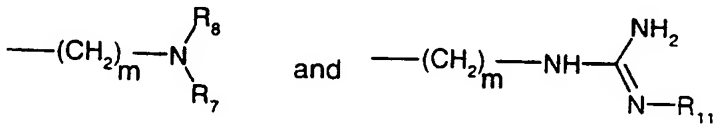
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;

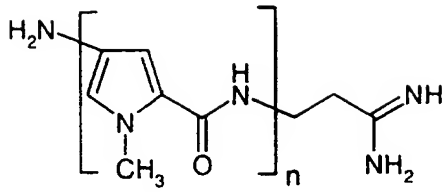
2-[1-methyl-4[1-methyl-4[1-methyl-4[4-(2-chloroethylsulfonyl)cinnamoyl-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine; and the pharmaceutically acceptable salts thereof.

5. A process for preparing the compounds of formula (I), and the pharmaceutically acceptable salts thereof, which process comprises:

(a) when B is other than

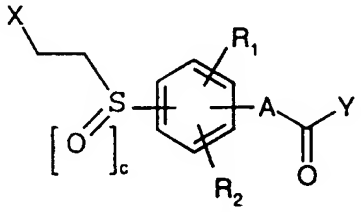


reacting a compound of formula:



(II)

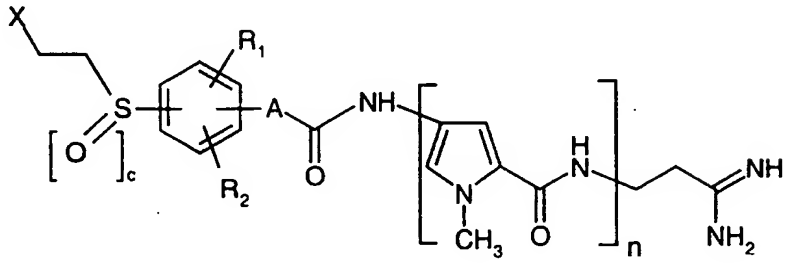
with a compound of formula:



(III)

wherein n, c, R_1, R_2, X and A are as defined in claim 1, and Y is hydroxy or a suitable leaving group;

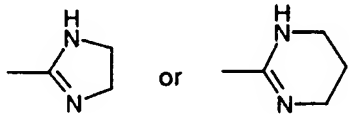
so as to obtain a compound of formula:



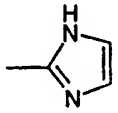
(Ia)

and, then, optionally reacting a compound of formula (Ia) with:

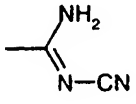
(i) $H_2N-(CH_2)_r-NH_2$, wherein r is 2 or 3, so as to obtain a compound of formula (I) having B equal to:



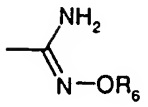
(ii) H_2N-CH_2-CHO, so obtaining a compound of formula (I) having B equal to:



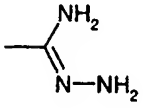
(iii) H_2N-CN, so obtaining a compound of formula (I) having B equal to:



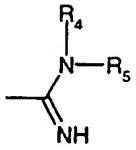
(iv) H_2N-OR_6, so obtaining a compound of formula (I) having B equal to:



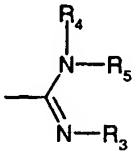
(v) H_2N-NH_2, so obtaining a compound of formula (I) having B equal to:



(vi) HNR_4R_5, so obtaining a compound of formula (I) having B equal to:



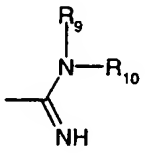
and then optionally with H_2NR_3, so obtaining a compound of formula (I) having B equal to:



(vii) succinic anhydride, so obtaining a compound of formula (I) having B equal to -C≡N;

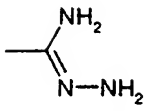
(viii) water in an alkaline medium, so obtaining a compound of formula (I) having B equal to $-CONR_9R_{10}$ wherein R_9 and R_{10} are both hydrogen atoms;

(ix) HNR_9R_{10}, so obtaining a compound of formula (I) having B equal to:

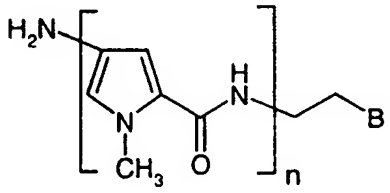


and then with water in an alkaline medium, so obtaining a compound of formula (I) having B equal to $-CONR_9R_{10}$, wherein R_9 and R_{10} are as defined in claim 1; or

(b) when B is other than

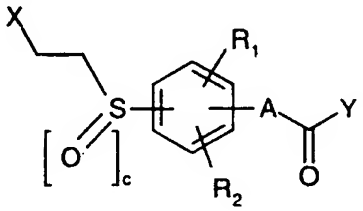


reacting a compound of formula:



(IV)

with a compound of formula:



(III)

wherein n, c, B, R_1, R_2, X, Y and A are as defined above; so obtaining the corresponding compound of formula (I); and, if desired, converting the compound of formula (I) into a pharmaceutically acceptable salt thereof.

6. A process according to claim 5 wherein, in the compounds of formula (III), Y is hydroxy or a group selected from chloro, 2,4,5-trichlorophenoxy, 2,4-dinitro-phenoxy, succinimido-N-oxy and imidazolyl.

7. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and/or diluents and, as the active principle, a compound as defined in claim 1.

8. A compound as defined in claim 1 for use in a method of treatment of the human or animal body by therapy.

9. A compound as defined in claim 8 for use as an antitumor agent.

10. Use of a compound as defined in claim 1 in the manufacture of a medicament for use as an antitumor agent.

INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/EP 99/05349

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 246 868 A (ERBA FARMITALIA) 25 November 1987 (1987-11-25) cited in the application abstract; claims 1,6-9 page 11; table page 15 -page 16; example 1 ---	1,7-10
A	WO 97 43258 A (PHARMACIA & UPJOHN SPA ;COZZI PAOLO (IT); BERIA ITALO (IT); CALDAR) 20 November 1997 (1997-11-20) cited in the application abstract; claims 1,5-10 page 24 -page 29; example 1 ---	1,7-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2000	26/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/EP 99/05349

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 28123 A (PHARMACIA & UPJOHN SPA ;COZZI PAOLO (IT); BERIA ITALO (IT); CALDAR) 7 August 1997 (1997-08-07) cited in the application abstract; claims 1,6-11 page 31 -page 37; example 1 -----	1,7-10

Form PCT ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. nal Application No
PCT/EP 99/05349

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0246868 A	25-11-1987	AT	80617 T	15-10-1992
		AU	597659 B	07-06-1990
		AU	7316387 A	26-11-1987
		BG	60531 B	28-07-1995
		CA	1314551 A	16-03-1993
		CS	9104137 A	16-09-1992
		DE	3781716 A	22-10-1992
		DK	254587 A	21-11-1987
		FI	872173 A,B,	21-11-1987
		GR	3006163 T	21-06-1993
		HK	31993 A	08-04-1993
		IE	60198 B	15-06-1994
		IL	82553 A	10-06-1991
		JP	1898111 C	23-01-1995
		JP	6023193 B	30-03-1994
		JP	62294653 A	22-12-1987
		KR	9511408 B	04-10-1995
		MX	9203122 A	01-07-1992
		NZ	220361 A	26-04-1990
		PT	84896 A,B	01-06-1987
		SG	3793 G	12-03-1993
		SU	1528316 A	07-12-1989
		US	5017599 A	21-05-1991
		US	5049579 A	17-09-1991
		US	5310752 A	10-05-1994
		ZA	8703593 A	12-11-1987
WO 9743258 A	20-11-1997	AU	2701697 A	05-12-1997
		EP	0912509 A	06-05-1999
		NO	985307 A	12-01-1999
		PL	329878 A	12-04-1999
WO 9728123 A	07-08-1997	AU	1596097 A	22-08-1997
		CA	2244139 A	07-08-1997
		EP	0880499 A	02-12-1998